REMARKS/ARGUMENT

Claims 1-4, 6-12, 14-15, and 17-28 are pending.

Claims 1-4, 6-9,11-12, and 17-28 have been amended.

Claims 5, 13, and 16 have been cancelled.

Applicants submit this paper with the correctly amended claims in response to the Official Communication of March 25, 2008, noting that claims 7 and 8 have been improperly amended. The presented herewith set of claims substitute the previous submitted set of claims. Applicants submit that the application is now in proper condition for examination.

Support for the amendments is found in the claims and specification (e.g., page 10, lines 1-8; page 11, lines 9-30; page 4, lines 16-38; page 7-9; the Examples) as originally filed. No new matter is believed to have been added.

In response to the objection to the specification, applicants submitted a Substitute Specification (marked up and clean copies) with the response filed December 7, 2007.

In response to the objection to Figures 2-3, applicants submitted Annotated and Replacement Figures 2 and 3, with the response filed December 7, 2007.

With respect to the objection to Figure 4, one gray is a basic unit of a radiation dose expressed in terms of absorbed energy per unit mass of tissue, i.e., 1 Gy (gray)=1J (Joule)/kg.

Applicants respond to the claim objections by correcting typographical errors.

Applicants request that the objections be withdrawn.

Applicants also submitted the Declaration of Joachim Fensterie with the response filed December 7, 2007.

In response to the rejection under 35 U.S.C. 101, applicants amended the claim to be directed to an isolated mammalian cell. Applicants request that the rejection be withdrawn.

Applicants further amended the claims in response to the rejection under 35 U.S.C. 112, second paragraph, and believe that the amended claims are not vague and indefinite. Applicants request that the rejection be withdrawn.

Claims 9-15 and 17-18 are rejected under 35 U.S.C. 112, first paragraph. The Examiner is of the opinion that the claims while being enabled for microphages and tumor cells infected with *S. typhimurium* and *Listeria monocytogenes*, are not enabled for a method of treatment of disorders.

The applicants are submitting herewith a declaration presenting the experiments conducted with *Listeria* infected 4T1 mice that carry tumors (*in vivo* model).

The question was to demonstrate that transgenic bacteria expressing a functional prodrug converting enzyme delivered via cells are enriched in the tumor tissue and can functionally convert the corresponding prodrug in tumor tissue samples. The product of the conversion, 6-Methylpurine (MeP), is toxic to tumor cells and the combined effect of the enrichment in the tumor tissue and successful conversion is therefore directly correlates to the efficacy.

To answer these question, the following method was applied:

a. A recombinant, attenuated *Listeria* strain (*L. monocytogenes* delta aroA) was constructed using standard molecular biology techniques encompassing a plasmid encoding the *E.coli* purimaucleotidephosphorylase (PNP) under the control of the CMV promoter active in eukaryotic cells (DNA delivery). This enzyme mediates the conversion of the prodrug 6-Methylpurine deoxyribose(MePdR) to MeP. The latter product is toxic for tumor cells.

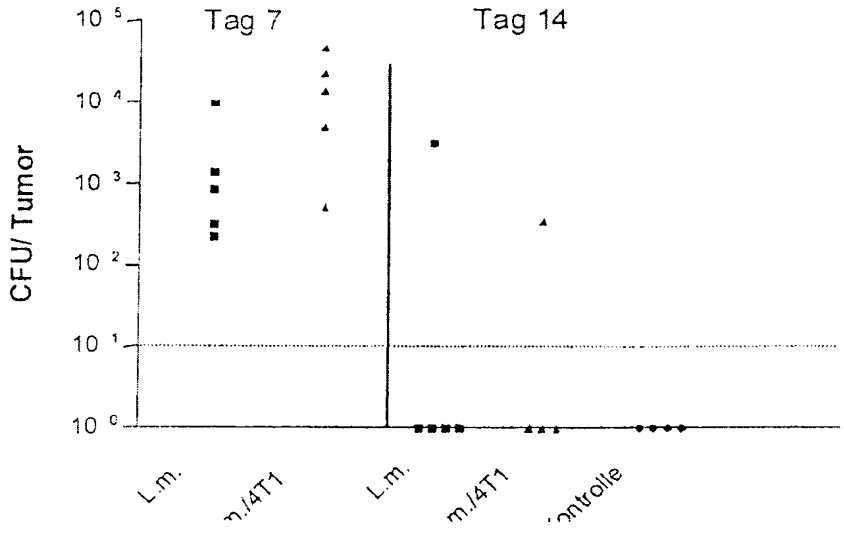
b. Animals were transplanted with 104 4T1 breast cancer cells. Tumors were allowed to grow up to a tumor diameter of approx. 0.5 cm before infection.

c. Animals were infected IV with $1.3x10^6$ recombinant *Listeria* or $2.0x10^7$ bacteria in irradiated 4T1 cells.

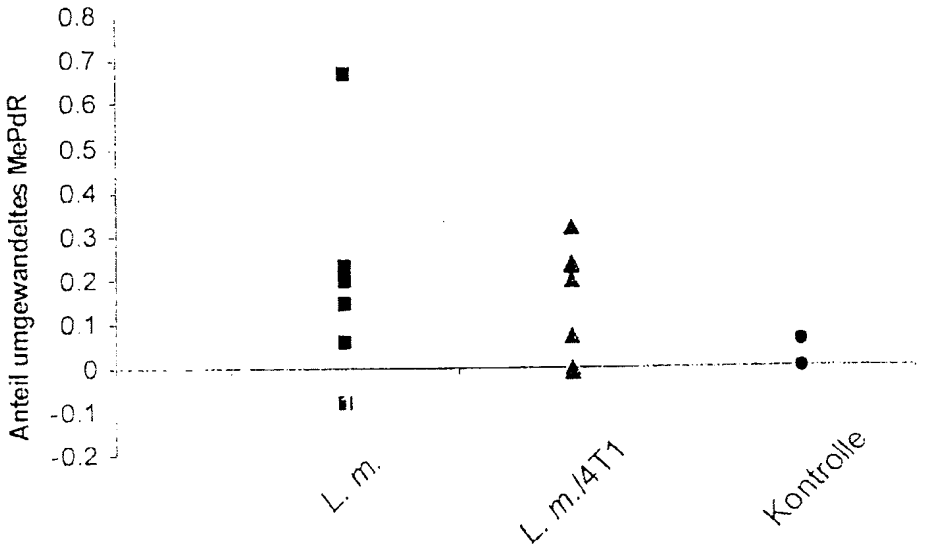
d. The CFU in the tumor tissue was determined by plating serial dilutions 7 days after infection.

e. 7 days after infection, the tumor was excised and homogenized. Tumor lysates were incubated for 48 h with the substrate MePdR. After incubation, the substrate conversion into MeP was assessed by HPLC. The results are expressed as relative amount of formed MeP.

10. The results depicted in the following figure demonstrate that the recombinant *Listeria* strain is effectively delivered into tumor cells in this experimental system (L.m., L.m./4T1, and Control).



The following picture encompasses the enzyme activity 7 days after infection. This picture demonstrates that the bacteria delivered by the irradiated cells can deliver the DNA into the tumor tissue which, in turn, is functionally transcribed in the eukaryotic target cells. As bacteria are both delivered into the tumor system by cellular carriers and the enzyme is active, the system is efficient for tumor therapy.



The experiments show that tumor of the animal model 4T1 mice is enriched with *Listeria* expressing a functional prodrug-converting enzyme, purine nucleoside phosphorylase (PNP). PNP converts purine pro-drugs to toxic metabolites that are known to cause reduction in tumor growth and prolonged survival. The cells infected with *Listeria* expressing PNP possess a higher enzyme activity and, therefore, a higher rate of pro-drug to drug conversion compared to controls. *See* Declaration of Joachim Fensterie with the response filed December 7, 2007.

Thus, the claims enabled for the prophylaxis and/or therapy of a disorder. Applicants request that the rejection be withdrawn.

A Notice of Allowance for all pending claims is requested.

Respectfully submitted,

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